

Direct Production of ^{99m}Tc on Canada's Existing Cyclotron Infrastructure

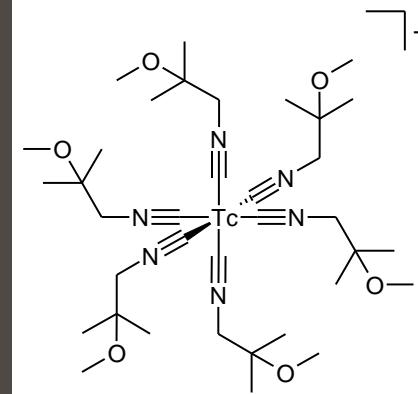
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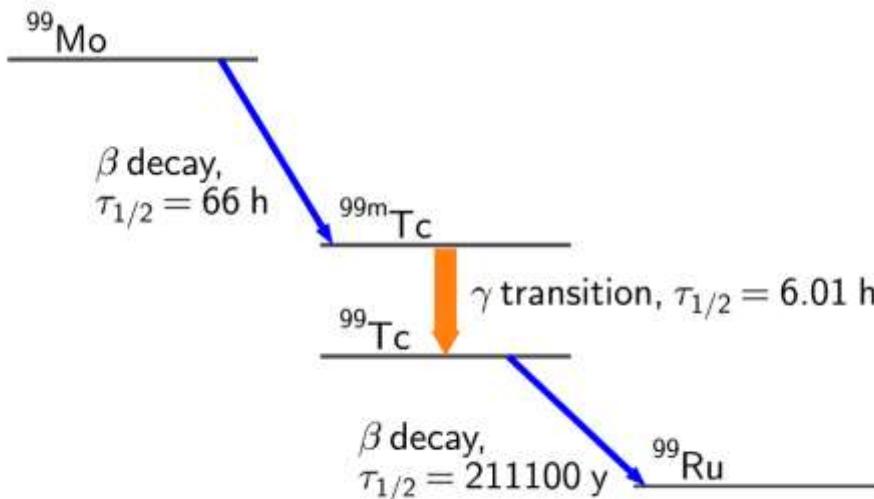


^{99m}Tc in Canada

- 80% of popⁿ lives within 150 Km of US border
 - 80% of popⁿ lives in urban mass across BC, AB, ON, and PQ
 - ^{99m}Tc usage rate of 4.5 - 5.7% of population (~35,000,000)
 - 1.55 - 1.96 million doses per year
 - 23,375 – 29,500 Ci annually
-
- Home of NRU, Maples
 - Current ^{99m}Tc production:
 - US: ~60%
 - Global: ~40%
 - Capacity: ~80%



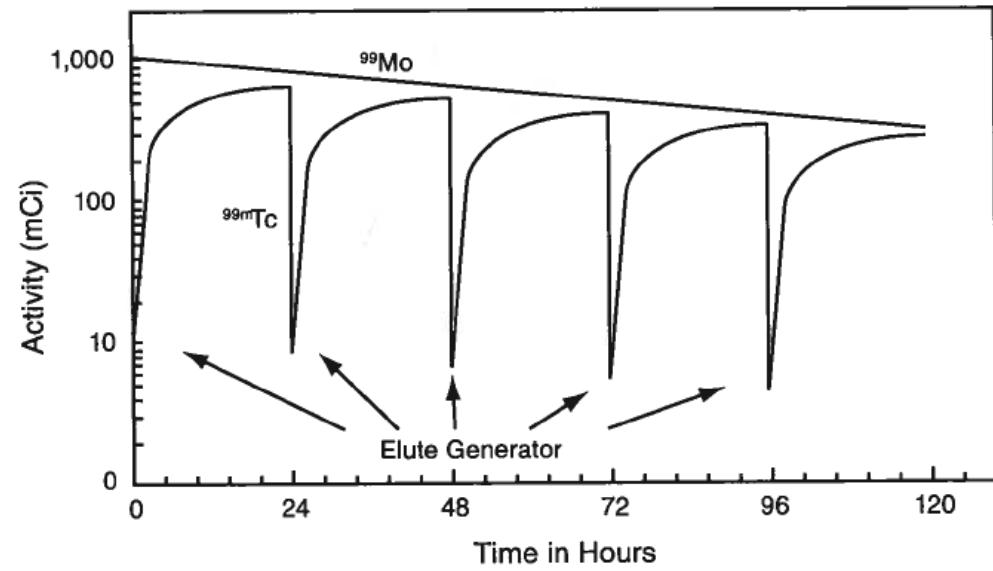
Current Paradigm: ^{99m}Tc Generators



- Transportable
- Easy to use

Tc-99m paradigm:

- Generators ‘milked’ daily
- ^{99m}Tc obtained as $^{99m}\text{TcO}_4^-$
- Kit based tracer production



Can alternatives meet this paradigm?

Alternatives for ^{99m}Tc production

- Alternatives are well known

Neutron ‘solution(s)’:



Photon ‘solution(s)’:



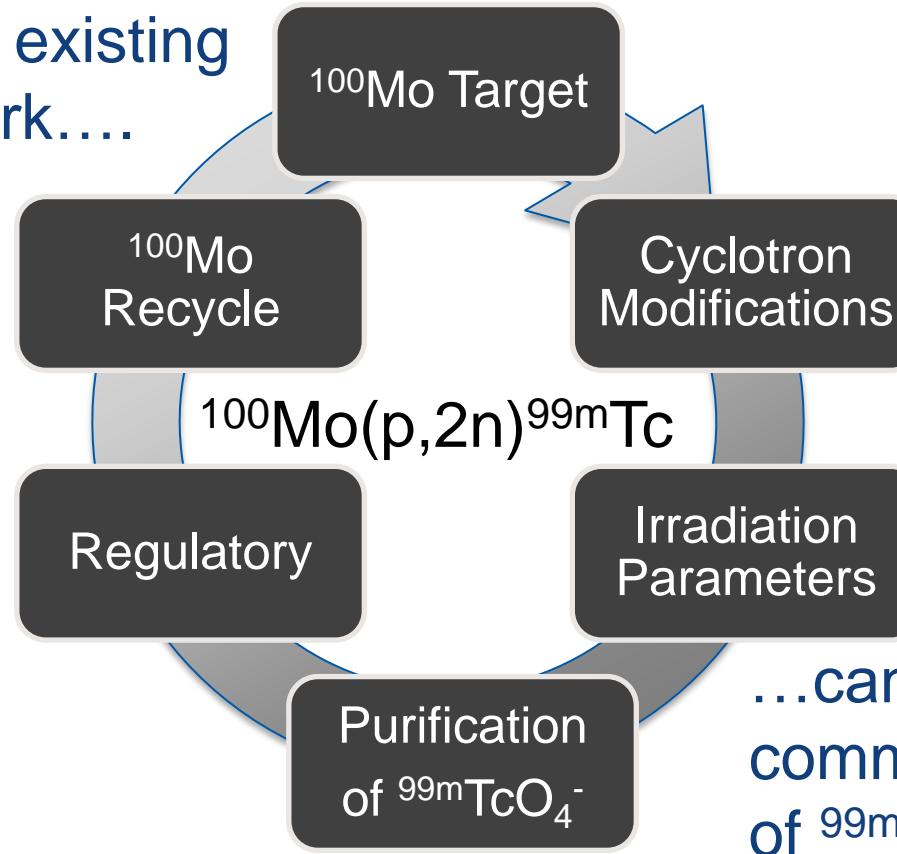
Proton ‘solution’:



All at various stages of feasibility/concept development

$^{100}\text{Mo}(\text{p},2\text{n})^{99\text{m}}\text{Tc}$ at the commercial scale

To demonstrate existing cyclotron network....



...can produce commercial quantities of $^{99\text{m}}\text{Tc}$

Goals: 1) Formulate policy on $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ isotope production
2) Demonstrate Feasibility/Concept

Team Equipment/Capabilities

- TR19 (vaulted), PETtrace (self-shielded, vaulted)



TR19
13-19 MeV, $\leq 200\mu\text{A}$
Upgrade to:
300 μA (approved)

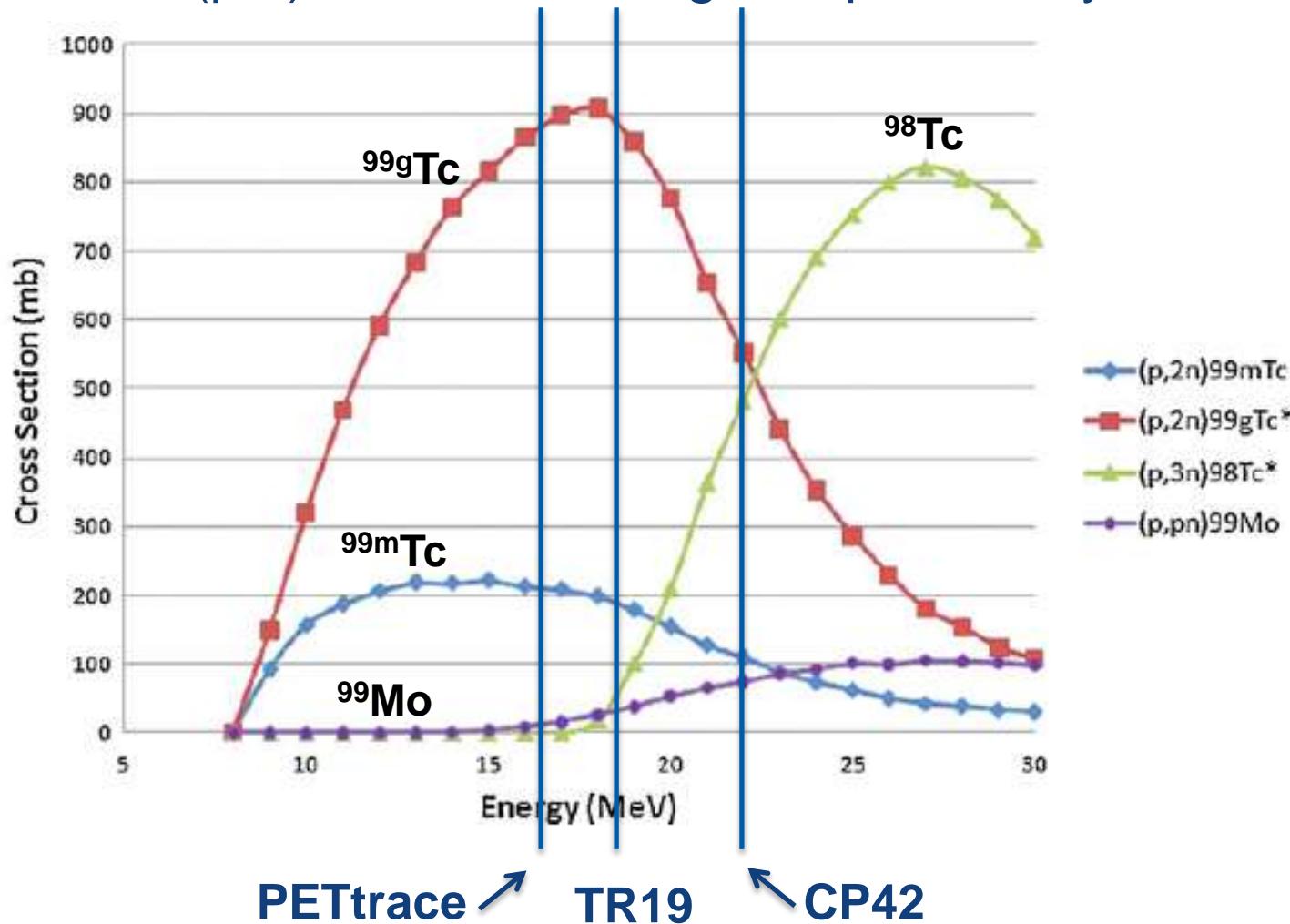


GE PETtrace
16 MeV, $\leq 100 \mu\text{A}$
Upgrade to: $\leq 150 \mu\text{A}$

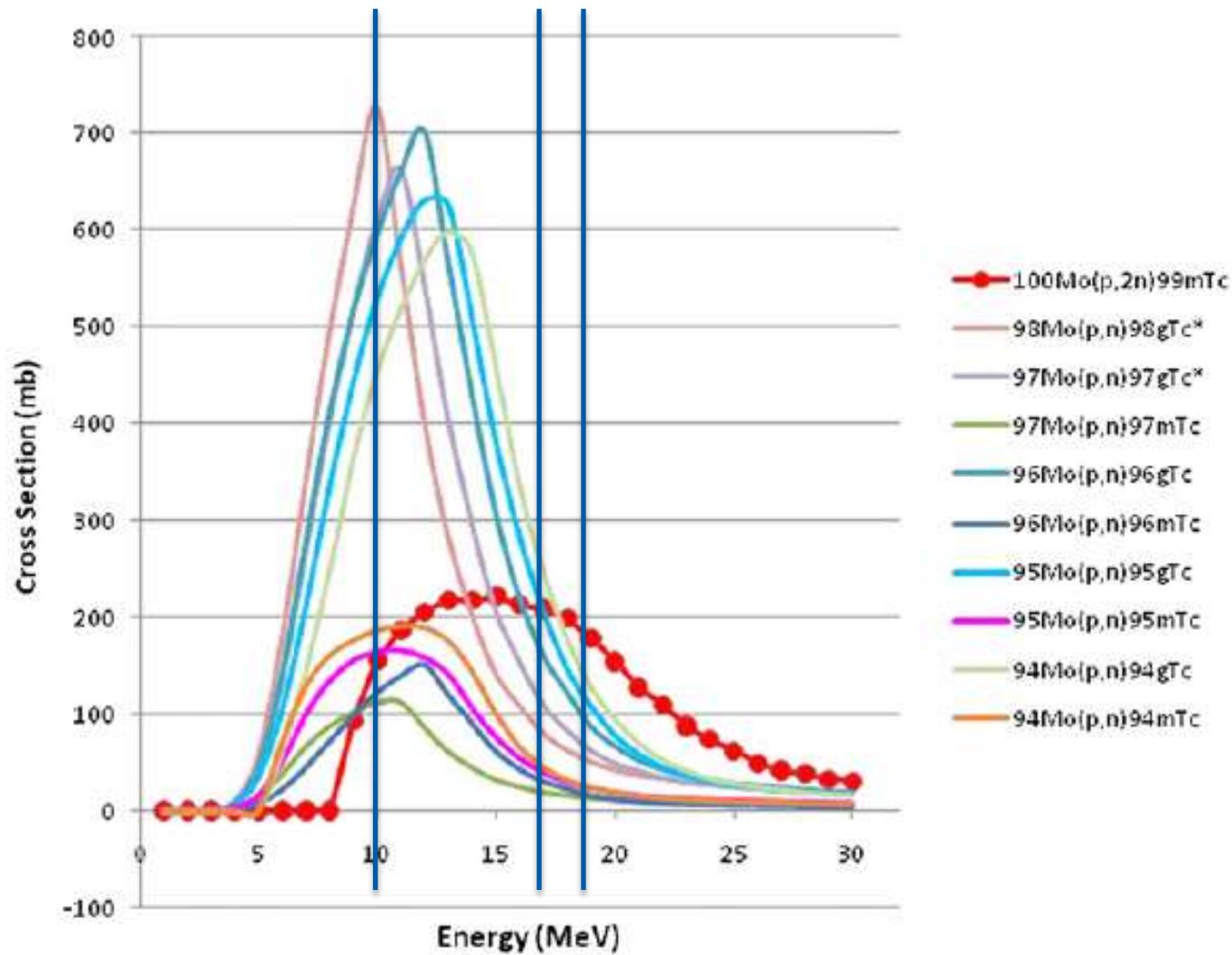
| Not shown: CP42, 20-42 MeV, $\leq 200\mu\text{A}$

Preliminary Assessment: Calculations

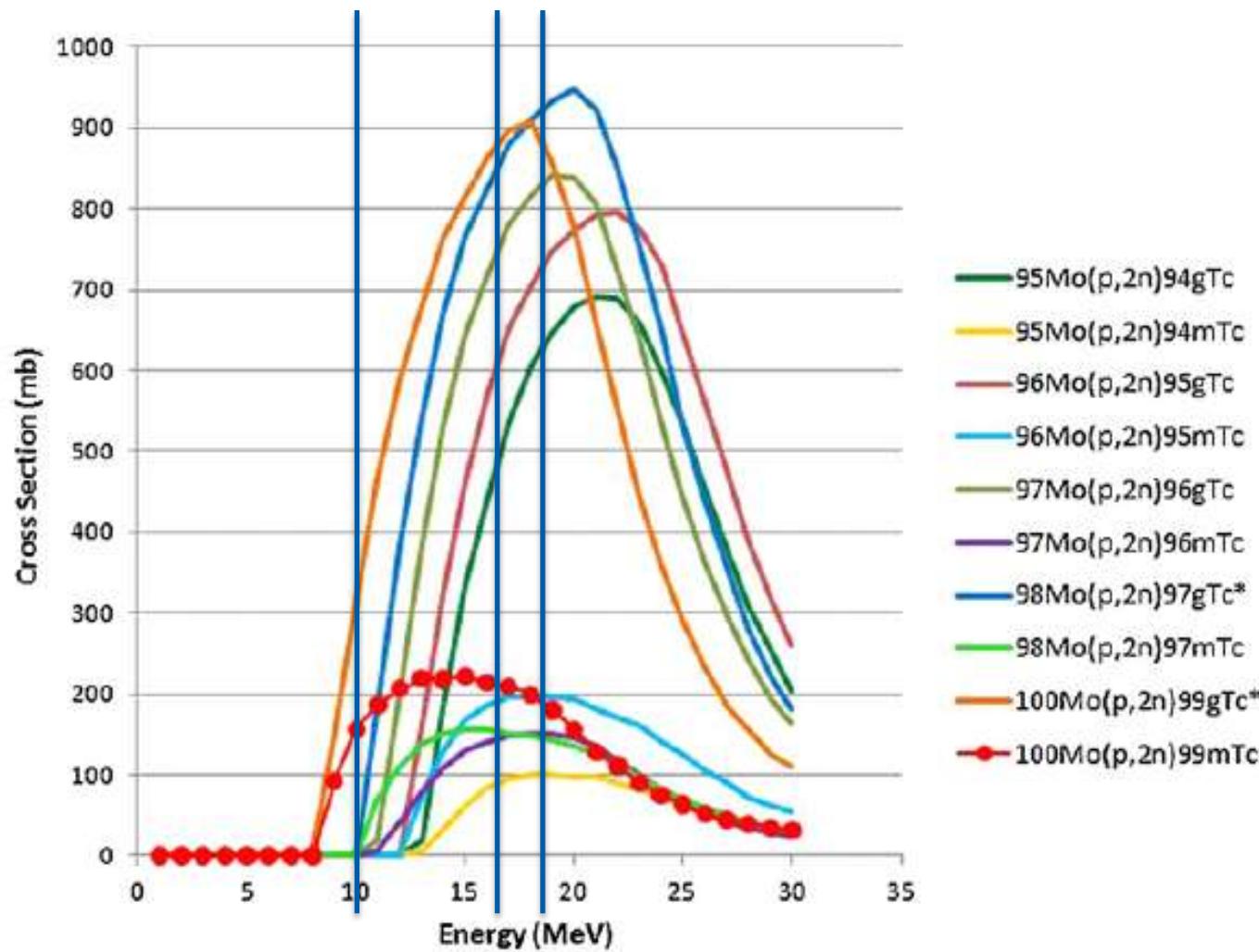
$^{100}\text{Mo}(p,x)$ reactions of highest probability



94-97Mo(p,n)

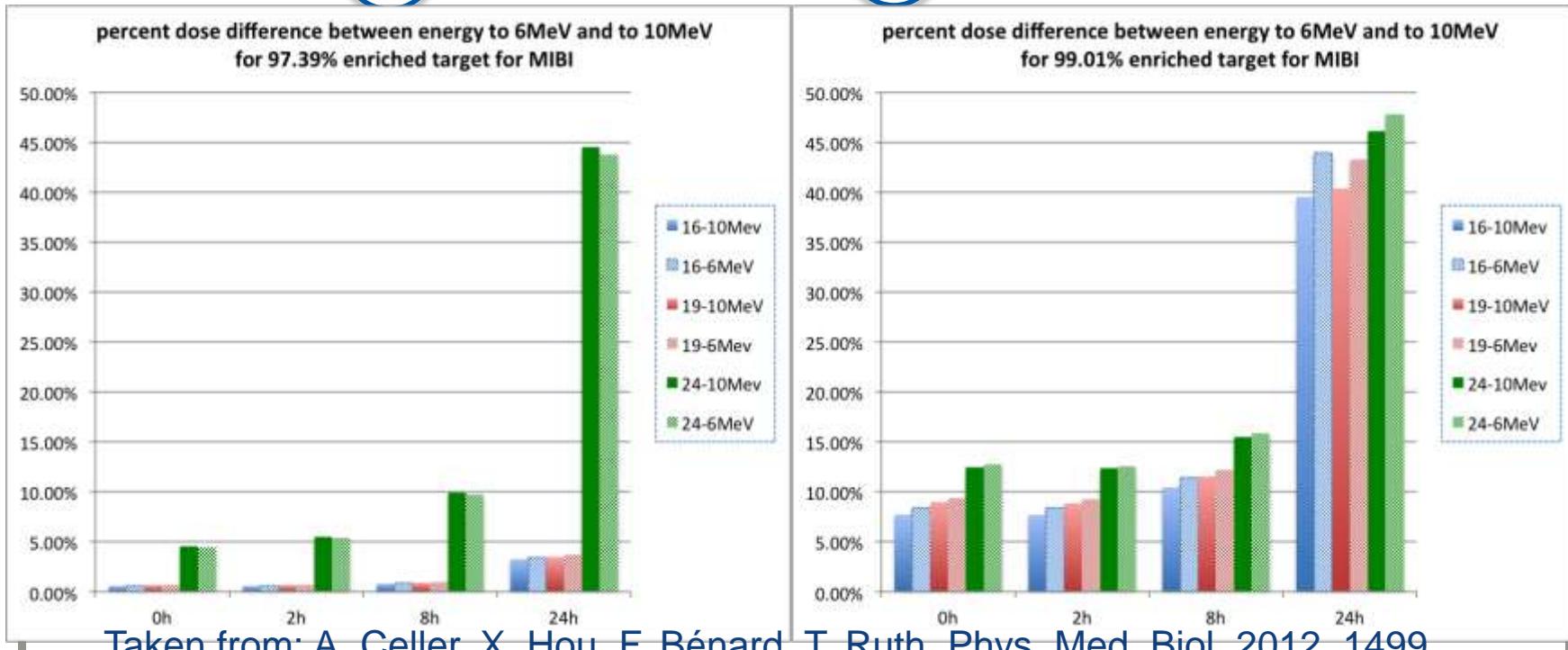


94-97Mo(p,2n) also contributes



Target Enrichment: Issues with lighter Mo isotopes

Isotope	Enriched				Natural
	A	B	C	D	
⁹² Mo	0.005	0.006	0.09	0.003	14.85
⁹⁴ Mo	0.005	0.0051	0.06	0.003	9.25
⁹⁵ Mo	0.005	0.0076	0.1	0.003	15.92
⁹⁶ Mo	0.005	0.0012	0.11	0.003	16.68
⁹⁷ Mo	0.01	0.0016	0.08	0.003	9.55
⁹⁸ Mo	2.58	0.41	0.55	0.17	24.13
¹⁰⁰ Mo	97.39	99.54	99.01	99.815	9.63



Taken from: A. Celler, X. Hou, F. Bénard, T. Ruth, Phys. Med. Biol. 2012, 1499

Critical Risk: ^{100}Mo Target Manufacturing

- Considerations
 - Mo is not amenable to electroplating
 - Power density/heat transfer
 - Ease of post irradiation workup
- Mass requirements:
 - Current: 80 and 300 μA and
 - Energy: 16 and 22 MeV – degrading beam to 10 MeV(?)
 - <300 to <660 μm (orthogonal) = 560 to 1240 mg per target
- Two manufacturing methods under evaluation

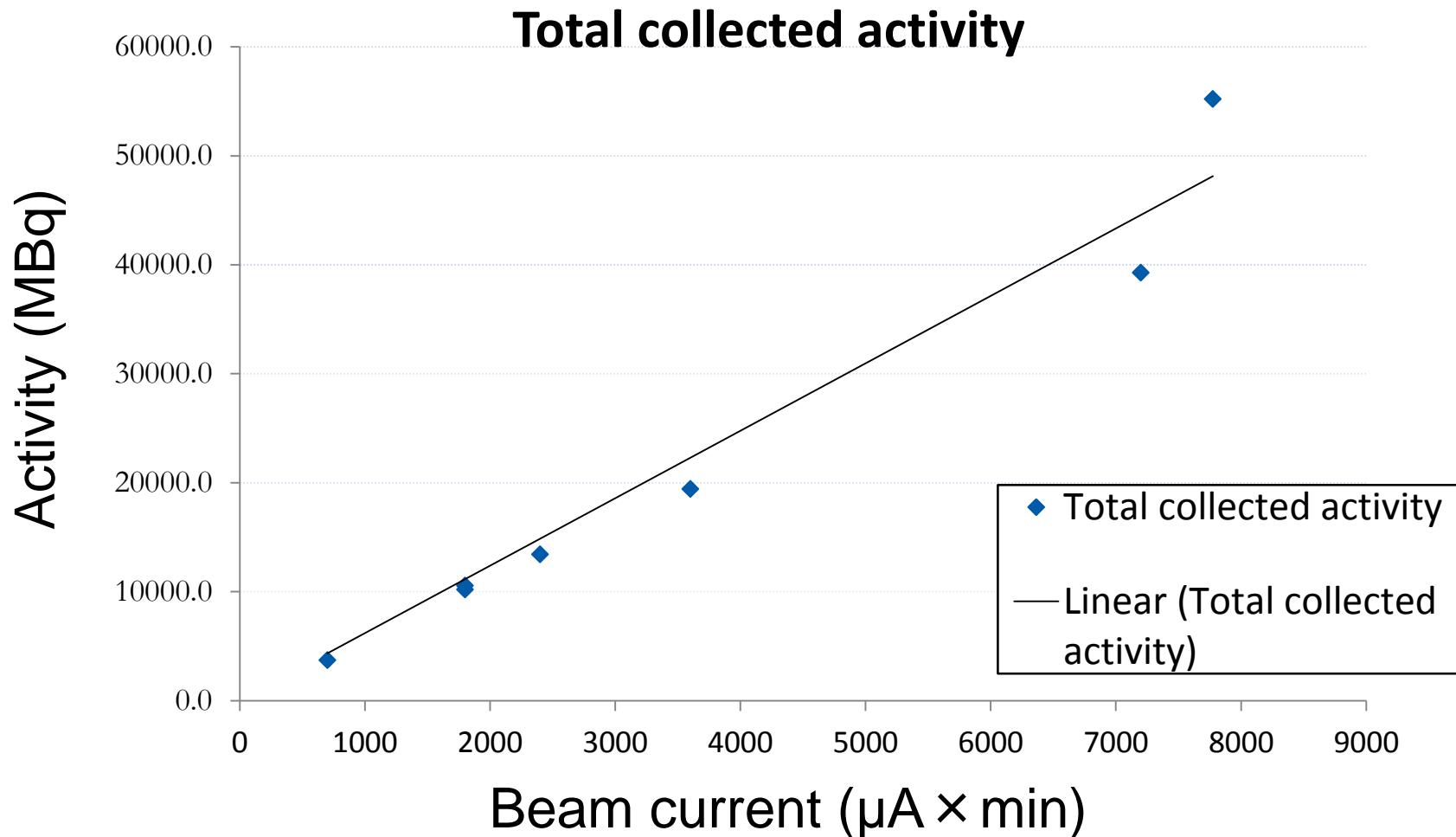


TR19 Solid Target System (BCCA)

- TR19 target assembly
- Progress (with Mo target process 1):
 - 100 μ A, 18 MeV on target (60 min)
 - Next: 200 μ A, 18 MeV on target (60 min)
 - Anticipated saturation yields of:
3.8 GBq/ μ A (103 mCi/ μ A)



BCCA Production Results – Total ^{99m}Tc



Note: Data points from target failure or thin target excluded

Radionuclidic Purity Results

(TR19, multiple irradiation times)

	Mo-100 (97.4%)		Mo-100 (99.01%)	
	Average	St. Dev.	Average	St. Dev.
Tc93	*	*	0.098%	0.031%
Tc93m	*	*	0.064%	0.088%
Tc94m	0.261%	†	0.655%	0.513%
Tc94	0.000%	†	0.096%	0.012%
Tc95	0.016%	0.005%	0.080%	0.011%
Tc95m	0.001%	0.001%	0.002%	0.003%
Tc96	0.022%	0.022%	0.018%	0.004%
Tc97m	0.000%	†	0.001%	0.001%
Tc99m	99.695%	0.206%	98.985%	0.610%
Mo99	0.000%	†	0.000%	0.000%
Nb95	0.005%	0.007%	0.001%	0.002%

* Not detected

† Detected in only 1 measurement

Current Pharmacopeia Requirements for ^{99m}Tc from Generators

REGULATORY REQUIREMENT	USP Fission	USP Neutron	EU Fission	EU Non-Fission
Mo-99 max %	0.015%	0.015%	0.10%	0.10%
Other max %		0.050%		0.01%
Other per dose		92 kBq		
I-131 %	0.005%		0.005%	
Ru-103 %	0.005%		0.005%	
Sr-89 %	0.00006%		0.00006%	
Sr-90 %	0.000006%		0.000006%	
Other beta/gamma	0.01%		0.01%	
Other alpha	0.0000001%		0.0000001%	

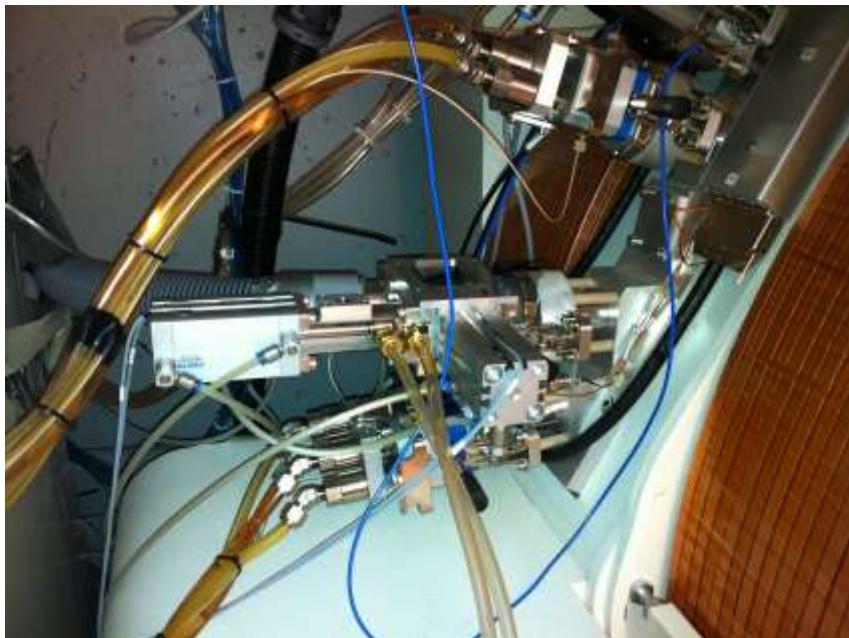
**Impurity ratings from (p,2n) approach are inconsistent
with current pharmacopeia requirements**

PETTrace Solid Target System

- PETtrace target assembly

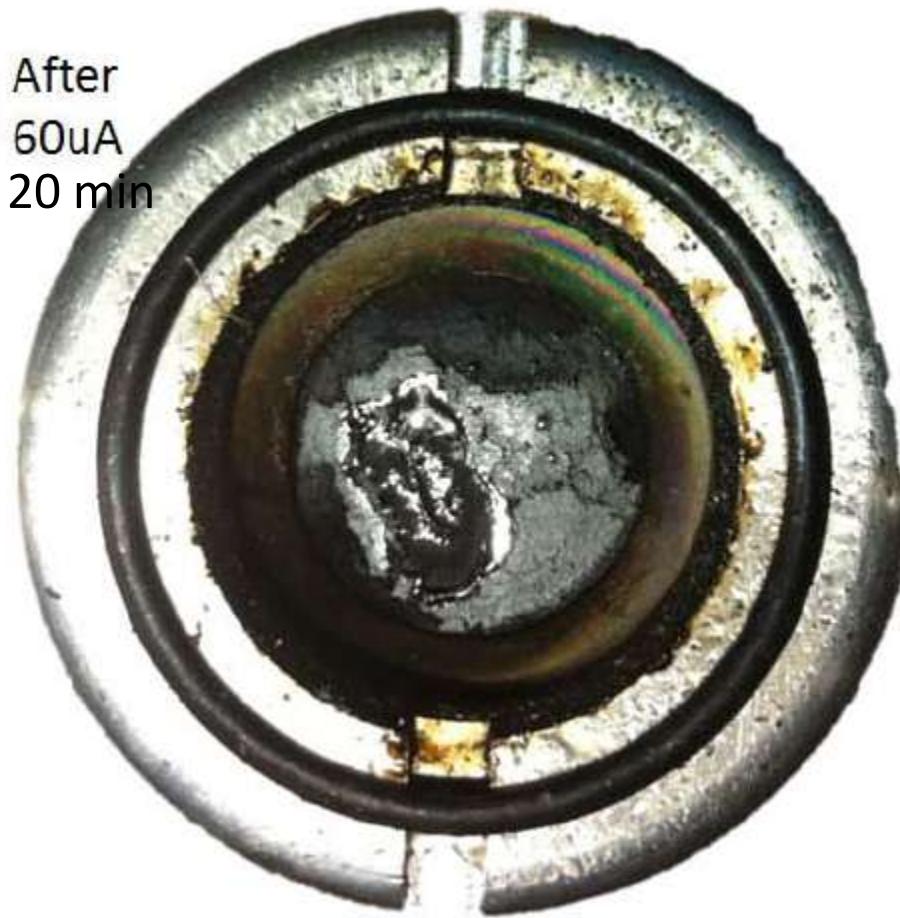
Progress to date (with pressed target):

- 100 μA , 16 MeV on target (60 min)
- Next: 130 μA , 16 MeV on target (60 min)
- Anticipated saturation yields of:
2.8 GBq/ μA (75.6 mCi/ μA)

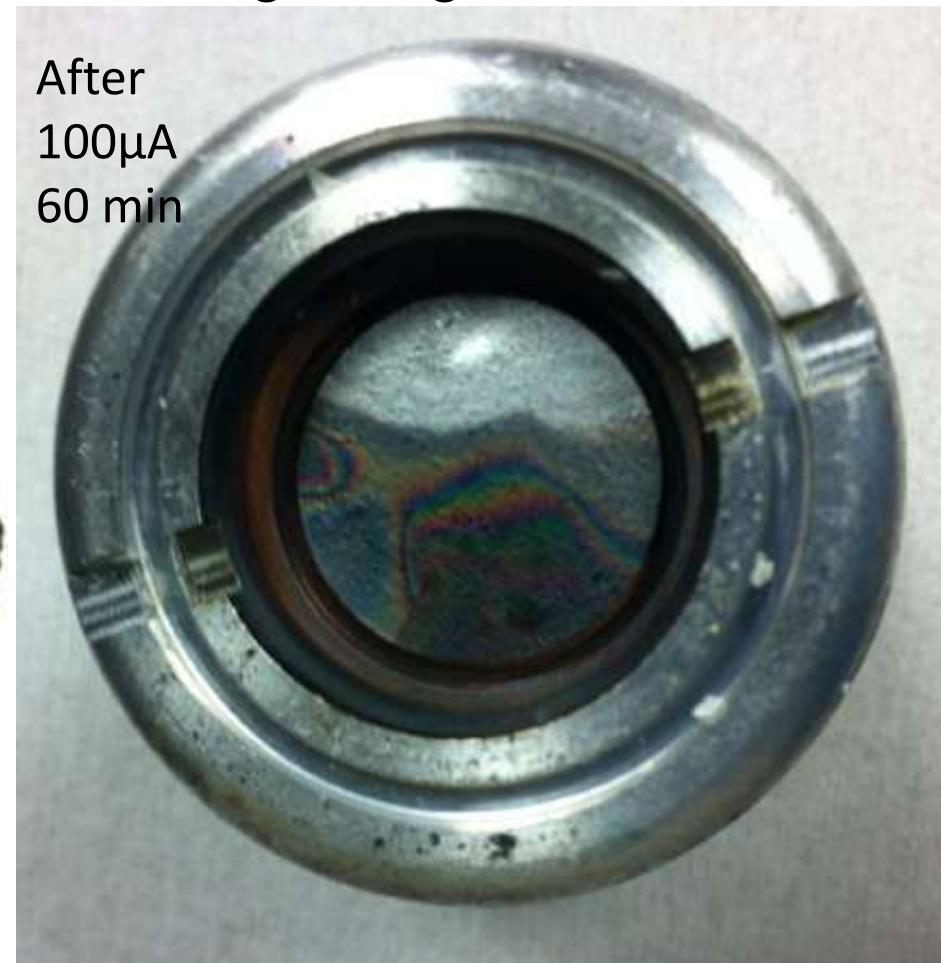


Target Testing

Target Mfg. Process 1



Target Mfg. Process 2



| Insufficient heat transfer causes Mo overheating

Radionuclidic Purity Results

(preliminary, GE PETtrace)

	Mo-100 (97.4%)		Mo-100 (99.01%)	
	Average	St. Dev.	Average	St. Dev.
Tc-93				
Tc-93m				
Tc-94m				
Tc-94				
Tc-95			0.108%	0.012%
Tc-95m			0.001%	0.0002%
Tc-96			0.015%	0.001%
Tc-97m				
Tc-99m			99.684%	0.210%
Mo-99**			0.68%	0.28%
Nb-95			0.012%	0.001%

Data Collection Underway

- Preliminary – data subject to change

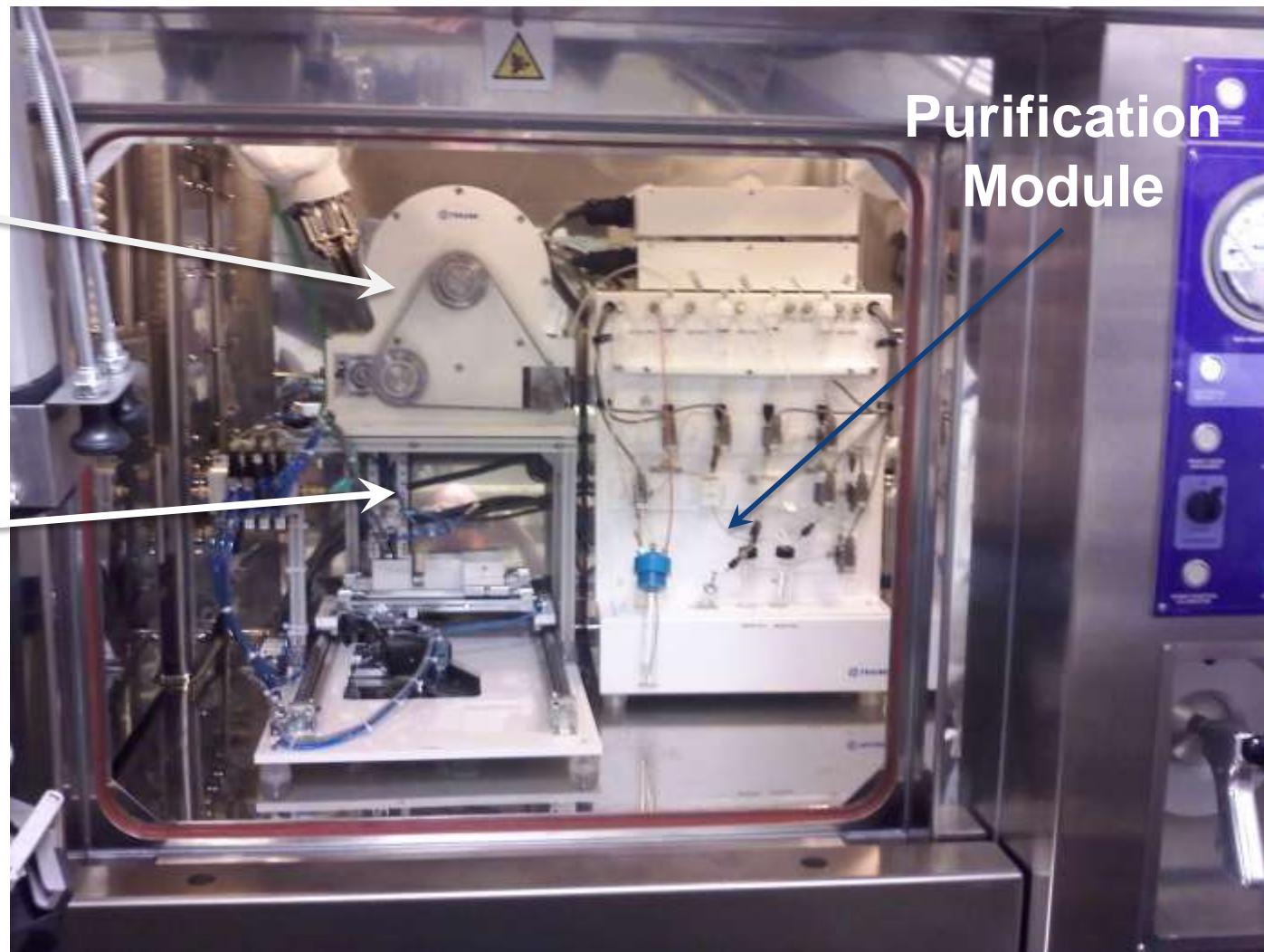
** Presence of ⁹⁹Mo due to purification method used

Target Transfer and Dissolution

Transfer
Drive

Receive
and
Dissolve

Purification
Module



Automated Isotope Purification

Remote-operated separation system



- **SPE-based method:**
 - Dowex™ vs ABEC
 - Many Alternatives
- **Process Time:** complete in 25 - 90 min.
- **Efficiency Range:** 70 to >95%
- **Radiochemical Purity:** >99.99% TcO₄
- **Trace analysis:** <10 Bq Mo-99, <5 ppm Al³⁺
- non-Tc impurities removed

**3 units built and distributed to partners
GMP compliant units purchased**

Inherent Resin Versatility: Numerous COTS options

Summary of Results

- Risk: Target manufacture process
- >37 GBq (1 Ci) produced at relatively low currents
- 5.48 MBq/(μ A·min) produced at 18 MeV
- >78% recovery efficiency of ^{99m}Tc -pertechnetate
- 3 types of kits (Sestamibi, HMPAO, MDP) radiolabeled successfully and passed standard QC ($n = 3$ each)
- Small amounts of ^{93}Tc , ^{94m}Tc , ^{94}Tc , ^{95}Tc , ^{96}Tc impurities were observed
- ^{95}Nb main by-product collected in waste along with Mo-100; negligible amounts in final product
- ^{100}Mo recycled with 85% recovery yield (range 80 – 92%)

Results Interpretation (so far)

- Production capacity: energy, time, current
 - Energy – intrinsic to machine (16-19 MeV, <22MeV)
 - Time – defined by other commitments (3-6 hrs)
 - Current – potential production boost (80-300+ μ A)
- ^{100}Mo isotopic purity is important
 - $^{95,96,97}\text{Mo}$ content is, perhaps, more important
- $^{99\text{m}}\text{Tc}$ specific activity needs regulatory consideration
 - Presence and affect on chemistry, dosimetry
 - Requires regulatory input (USP, EP)
- Cost estimates: as low as \$7.80-\$8.10 / dose
 - Brownfield estimate

Efforts until 2016

- Hardware optimization
 - High current irradiations (up to 300 μ A)
 - Demonstrate yields over 370 GBq (10 Ci).
- Implement (GMP) purification method
- Refined assessment of radionuclidic purity
- Reliability assessments
- Set acceptance criteria for ^{100}Mo isotopic composition
- Regulatory Documentation
- Clinical Trials (CTA)
- NDS submission to Health Canada

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Thank you!

Merci



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